PATENT
Atty. Docket No.: 02307E-080710US
Client Ref. No.: UC 97-262-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Emil A. Tanagho
Rajvir Dahiya
Tom F. Lue

Application No.: 10/052,889

Filed: January 18, 2002

For: ACELLULAR MATRIX GRAFTS: PREPARATION AND USE

Customer No.: 20350

Confirmation No. 3329

Examiner: Prebilic, Paul B.

Technology Center/Art Unit: 3738

APPELLANTS' BRIEF UNDER 37 C.F.R. §41.37

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This brief is filed pursuant to 37 C.F.R. §41.37, following the Notice of Appeal filed on September 1, 2006. A petition to extend time for one month, from November 1, 2006, to December 1, 2006, is filed concurrently. Also submitted with this brief is the authorization to pay the fee as set forth in 37 C.F.R. §41.20(b)(2).

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I. REAL PARTY IN INTEREST

The real party in interest in U.S. Application No. 10/052,889 is the Regents of the University of California.

II. RELATED APPEALS AND INTERFERENCES

There are no other pending appeals by Appellant or interferences in which Appellant is involved, the outcome of which would directly affect the decision by the Board of Patent Appeals and Interferences in this pending appeal.

III. STATUS OF THE CLAIMS

Claims 1-23 were originally filed. Subsequently, claims 24-28 were added and claims 1-23 were canceled. Claims 24-28 are pending in this application. In the final Office Action mailed March 6, 2006, the Examiner rejected claims 24-28 under 35 U.S.C. §103(a), alleging that the claimed invention is obvious over Bishopric (U.S. Patent No. 5,855,620) or Goldstein (U.S. Patent No. 5,632,778) in view of Gregory (U.S. Patent No. 5,990,379). Claims 24-28 were also rejected under the judicially created doctrine of obviousness-type double patenting over the claims of U.S. Patent No. 6,371,992. The rejection of claims 24-28 under 35 U.S.C. §103(a) for alleged obviousness is being appealed.

IV. STATUS OF THE AMENDMENTS

No amendment was filed subsequent to the final Office Action of March 6, 2006.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter in this appeal relates to a novel tissue matrix graft, which is derived from the smooth muscles of ureter or urethra and useful for

repairing damaged ureter or urethra. This matrix is unique in that, while it is essentially an accelluar intact framework of collagen and elastic fibers, it retains water impermeability of the original ureter or urethra tissue and permits growth of muscle cells within the collagen/elastin framework.

Claim 24

The subject matter claimed in independent claim 24 is an insoluble elastic matrix graft for repairing ureter or urethra smooth muscle. This matrix graft has the following properties: (i) the matrix graft is derived from ureter or urethra smooth muscle tissue; (ii) the matrix graft is impermeable to urine; (iii) the matrix graft consists essentially of an intact framework of collagen and elastic fibers that is free of cell contents; and, (iv) the framework permits growth of muscle cells within the framework. Support for this claim can be found in the specification, *e.g.*, on page 3, lines 2-5, 19-22, on 28-32, on page 6, lines 18-24, and also on page 9, lines 14-15.

VI. GROUNDS OF REJECTION TO BE REVIEWED AND APPEALED

1. Claims 24-28 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Bishopric (U.S. Patent No. 5,855,620) or Goldstein (U.S. Patent No. 5,632,778) in view of Gregory (U.S. Patent No. 5,990,379).

VII. ARGUMENT

The Rejection for Obviousness Is Improper

Claims 24-28 stand rejected under 35 U.S.C. §103(a) as the Examiner alleges that the claimed invention is obvious over Bishopric (U.S. Patent No. 5,855,620) or Goldstein (U.S. Patent No. 5,632,778) in view of Gregory (U.S. Patent No. 5,990,379). Appellant respectfully traverses the rejection and argues that the rejection is improper.

1. Standard to Assess Obviousness

According to MPEP §2143, to properly raise an obviousness rejection, the Examiner must carry the initial burden by meeting three requirements: first, all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; second, there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and third, there must be a reasonable expectation of success in making such a combinations.

Once the Examiner properly discharges his initial burden and establishes a *prima facie* case of obviousness, the burden shifts to the patent applicant to rebut the *prima facie* case by providing arguments and/or evidence, which may include evidence that the claimed invention yields unexpected improved properties or properties not present in the prior art. MPEP §2144.08 II.B. After the applicant presents the rebuttal evidence, the Examiner should reconsider any initial obviousness determination in view of the entire record. MPEP §2144.08 III.

2. The Claimed Invention, Cited References, and Inventor's Declarations

As characterized above, the claimed invention relates to an insoluble elastic matrix graft for repairing ureter or urethra smooth muscle. This matrix graft has the following properties: (i) the matrix graft is derived from ureter or urethra smooth muscle tissue; (ii) the matrix graft is impermeable to urine; (iii) the matrix graft consists essentially of an intact framework of collagen and elastic fibers that is free of cell contents; and, (iv) the framework permits growth of muscle cells within the framework.

In contrast, the primary references, Bishopric and Goldstein, teach how to make a collagen/elastin matrix or bioprothesis from tissues such as skin and heart valve, whereas the secondary reference, Gregory, teaches how to extract and purify elastin from various tissues including ureter.

During the prosecution, two declarations were submitted under 37 C.F.R. §1.132 by Dr. Emil Tanagho, a named inventor on this application, to establish that, first,

the cited references do not provide a motivation or suggestion to combine the claim limitations; second, there is no reasonable expectation of success to arrive at the claimed invention by combining the teaching of the cited references; and third, the claimed graft matrix has unexpected properties, which serves as evidence to rebut a *prima facie* case of obviousness, if assuming that the Examiner has established one.

3. There Is No Motivation to Combine the Claim Limitations

In the first declaration submitted with Appellant's response of December 16, 2005 ("Declaration I"), Dr. Tanagho explains why there is no motivation to combine the teaching of the primary references (Bishopric and Goldstein) and the secondary reference (Gregory): the primary references relate to an acellular collagenous matrix, whereas the secondary reference relates to elastin extraction and purification. Because of the distinct results achieved by the processes, one of skill in the art would not be motivated to combine these references. See paragraph 6 of Declaration I.

The pending claims of this application are directed to a collagen/elastin matrix derived from ureter or urethra smooth muscles, thus, in paragraphs 7-9 of the declaration, Dr. Tanagho provides an introduction of the important distinctions between the properties of elastin and collagen, as well as the methods for their extraction or preservation. According to Dr. Tanagho, under a light microscope, collagen and elastin form a matrix of interwoven fibers. Under an electron microscope, both collagen and elastin individually form their own fibrous matrix. These two proteins have distinct characteristics and thus contribute to different aspects of the collagen/elastin matrix: collagen imparts strength and elastin imparts flexibility. Collagen, a fibrous protein consisting of a combination of types I, II, III, *etc.*, is readily solubilized by conditions that do not appreciably solubilize elastin. When present within a matrix, collagen derives its strength to a large extent from the length of the fibers. Furuto *et al.* (made of record with Appellant's response of May 3, 2005, as Exhibit 2) describe a preferred method of

solubilizing collagens, where selective extraction of collagen involves using salt and diluted acid (*see, e.g.*, pages 43-44).

On the other hand, elastin and its purification procedures are described in the review articles by Rosenbloom (made of record with Appellant's response of May 3, 2005, as Exhibit 3) and Soskel *et al.* (made of record with Appellant's response of May 3, 2005, as Exhibit 4). According to Rosenbloom, the fibers of elastin are called elastic fibers, which are 90% elastin and 10% microfibrillar components. Soskel *et al.* also describe elastin as a "heavily cross-liked meshwork, perhaps best described as a fiber rather than as a protein. It is an infinitely large polymer" (*see, e.g.*, page 196). The flexibility of elastin is due to its extensive crosslinking between polypeptide strands.

In the present application, the claimed matrix is a collage/elastin matrix that maintains its native strength and flexibility. This means that the fiber lengths and cross-linking have not been chemically altered to weaken the integrity of the matrix. The matrix is also intact in that it can retain urine and does not have rips or tears through which urine can pass.

Regarding the references cited by the Examiner, Dr. Tanagho points out in paragraph 10 of the declaration that, among the two primary references (Bishopric and Goldstein) cited to form the basis of the obviousness rejection, the Bishopric reference describes a generic method for producing a collagen/elastin matrix from tissues, where the descriptions generally relate to body tissues, with focus on vascular tissues such as heart valves. This is the most apparent in the examples of this reference. Similarly, the Goldstein reference describes bioprothesis derived from tissues following a decellularizing process involving enzymatic treatment. The specific tissue types discussed in this reference are skin and heart valves, although the author does not limit his invention to these tissue types.

Dr. Tanagho further discusses the secondary reference by Gregory in paragraph 11 of the declaration: the Examiner apparently took the position that this

missing limitation, *i.e.*, deriving a collagen/elastin matrix from ureter or urethra smooth muscle tissue, can be found in the Gregory reference. The Gregory reference teaches methods for elastin extraction and purification from various sources, including ureter. This reference, however, describes its matrix as an "elastin matrix" rather than a "collagen/elastin matrix." Elastin is *per se* a "matrix." There is no indication that the methods disclosed by Gregory are preserving the natural collagen/elastin matrix present in tissues such as in the ureter or urethra smooth muscles. For instance, the extraction conditions described by Gregory (column 5, lines 36-55) make no allowance for preserving the collagen or microfibrillary components. Gregory describes the conventional methods for elastin extraction/purification, which call for acid and base treatment and/or use of heat. Under these conditions, collagen fibers will be severely damaged, if not completely solubilized. In fact, it is explicitly stated in EXAMPLE 3 (column 11, lines 46-58) that the elastin-based biomaterials produced according to the method taught therein "appear translucent, pearly white in color and collapsed when removed from water ***indicating the absence of collagen*** and other structurally supportive proteins" (emphasis added).

Thus, Dr. Tanagho concludes that because of the difference in purpose and in result of the methods taught by Bishopric or Goldstein and by Gregory, a person of ordinary skill in the art would not find any suggestion or motivation from these references to combine the limitations found in these references. Gregory teaches extraction of elastin in a process far too harsh to preserve the intact collagen/elastin scaffolding. An artisan who sets out to prepare a bioprothesis described by Bishopric or Goldstein would find no reason, either in the references or elsewhere, to combine the disclosure of Gregory, as the latter teaches the disruption of the collagenous network and would therefore defeat the purpose of preparing a implantable material having required structural integrity. See paragraph 12 of Declaration I.

Appellant thus contends that the Examiner has not met the second requirement for establishing a *prima facie* case of obviousness.

4. There Is No Reasonable Expectation of Success

Dr. Tanagho also explains in Declaration I that there would be no reasonable expectation of success even if an artisan were somehow inspired to combine the teaching of Bishopric or Goldstein with the teaching of Gregory, and attempted to produce a collagen/elastin matrix derived from tissues other than those actually experimented by Bishopric and Goldstein, there would be no reasonable expectation of success in obtaining such a matrix with the properties as defined in the present application. Dr. Tanagho indicates that this is because there exists significant difference in properties between ureter/urethra smooth muscle and other tissue types used in the methods described by Bishopric or Goldstein. See paragraph 13 of Declaration I.

According to Dr. Tanagho, as far as the applicability of the disclosed methods is concerned, Bishopric and Goldstein appear to encompass a whole universe of tissue types. Yet, besides the certain tissue types that have been shown in the examples, these two references do not adequately address the feasibility of their methods in other tissues, particularly those with special properties due to their distinct structure and functionality (*e.g.*, the properties of flexibility and water impermeability of the ureter and urethra) and the ability to serve as an organ-specific scaffold for a recipient's re-growth of the same organ's cellular content and muscular tissue. There is a large number of different types of tissues present in a human body, and the tissues differ drastically in terms of strength, elasticity, and porosity of the cellular matrix. For instance, heart valves are a type of highly specialized tissue in that the tissue is nearly acellular except for a thin external layer of cells that can be readily removed by a variety of treatment methods to achieve a thick, dense, and relatively stiff matrix. In contrast, the intact matrix of smooth muscles such as that forms ureter or urethra provides a waterproof sheath with much higher flexibility. The matrix taught by Bishopric or Goldstein cannot substitute the matrix provided by the present disclosure, because the matrix of the present invention provides some important features that cannot be predicted or expected from the teaching of the cited references: first, the matrix of the present invention must be strong enough

retain fluids without leakage, even when under pressure; second, the matrix must be flexible enough to accommodate changing fluid pressure; third, the matrix can be sutured without compromising its internal integrity or tearing when under pressure; and fourth, the matrix must be able to sustain growth of multiple cell types (muscle, epithelial, mucosal, and nerve) necessary to restore function to the repaired organ. See paragraph 14 of Declaration I.

Appellant thus contends that the Examiner has not met the third requirement for establishing a *prima facie* case of obviousness.

5. The Claimed Matrix Has Unexpected Properties

Even assuming that a *prima facie* case of obviousness is established, it is effectively rebutted by evidence presented in Declaration I. To this end, Dr. Tanagho offers clinical data to demonstrate that the surprising and extraordinary properties of the claimed acellular matrix graft of this application. Because such properties simply cannot be expected from combined reading of the cited references, Dr. Tanagho contends that the present invention is not obvious over the cited references.

In paragraph 16 of Declaration I, Dr. Tanagho attests that the collagen/elastin matrix of the present invention has been shown, in actual testing and use, to possess extraordinary properties that cannot be predicted from the cited references. Dr. Tanagho points out that the inventors of this application have successfully accomplished the goal of making a matrix that has preserved the native collagen/elastin scaffolding and thus maintained the desired strength and flexibility. This matrix has no antigenicity and readily permits cell repopulation into the collagen/elastin framework. These properties of the matrix as a tissue graft have been tested in numerous studies and the graft has consistently performed well. This is evidenced by Sievert *et al.* (made of record with Appellant's response of May 3, 2005, as Exhibit 5). Three additional publications by the present inventors provide further details in the surprisingly outstanding quality of the ureter/urethra-derived collagen/elastin matrix that allowed

successful graft and long term use. The performance of the matrix is particularly remarkable in terms of recellularization and pressure profile (Dahms *et al.*, *Urology* **50**:818-825, 1997; Sievert *et al., J. Urol.* **163**:1958-1965, 2000; and Sievert *et al., J. Urol.* **165**:2096-2012, 2001, made of record with Appellant's response of May 3, 2005, as Exhibits 6-8, respectively).

In paragraph 17 of Declaration I, Dr. Tanagho introduces dramatic evidence (slides 1-11, presented as Exhibit B) to show that recent effort by the present inventors using the claimed matrix graft for repairing urethra in human patients has proven highly successful. In particular, the claimed invention was used by the inventors on a human subject to correct damaged urethral tissue. More recently, others have referred to the inventor's procedure and copied successfully on patients around the world. The eleven (11) slides attached to Declaration I describe some aspects of the procedure. Slide 1 shows the stenosed (damaged or strictured) urethral tissue that was replaced. Slide 2 shows an x-ray of the stenosed (damaged or strictured) segment of the urethra. Slide 3 shows a chart and numbers of the patient's urine flow before the operation. Slide 4 shows a sketch of the operation. Slide 5 shows the patient's pre-operation condition. Slide 6 shows the donor's (cadaveric) urethral tissue to be grafted into the patient, which donor's tissue was treated using the same process described in this patent application. Slide 7 shows the patient's urethral tissue to be removed. Slide 8 shows the cadaveric tissue of the appropriate size that was treated using the process described in this patent application to be grafted into the patient. Slide 9 shows the sutured donor's tissue implanted into the recipient. Slide 10 shows an x-ray of the grafted urethral tissue of the healthy recipient after the operation. Slide 11 shows a chart and numbers of the healthy recipient's normal urine flow after the operation. This surgical procedure typically involves exposing the stenosed urethral segment and splitting it open ventrally. The cadaveric decellularized urethra is also split open and the appropriate length and width isprepared to be used as an onlay graft over the stenosed urethral segment using 50 absorbable sutures and all the wounds are then closed in the usual manner.

In contrast to the proven success achieved by the matrix graft of this invention, Dr. Tanagho states, a matrix produced from any randomly selected tissue type, including those that have been used by Bishopric and Goldstein, simply cannot be expected to possess the exceptional properties of the matrix graft of the present invention, which are essential for the successful repair of ureter or urethra. The combined teaching by Bishopric or Goldstein and the teaching by Gregory, does not show or suggest use of the decellularized tissue as an organ-specific scaffold for re-growth of specific organs' cellular contents and muscular tissues. See paragraph 18 of Declaration I.

Appellant thus contends that, even assuming that the Examiner properly has established a *prima facie* case of obviousness, it has been effectively rebutted by the evidence presented in Declaration I.

6. The Examiner Has Not Properly Considered the Rebuttal Evidence

i. Motivation to Combine

In spite of the evidence and explanations presented in Declaration I, the Examiner sustains the obviousness rejection in the final Office Action of March 6, 2006.

The Examiner first argues that the motivation to combine Gregory with the primary references stems from the general desire to replace damaged tissue with the same type in a patient. The Examiner also argues that the references all come from the same field of endeavor, one would therefore be motivated to use the method taught in the primary references to make ureter tissue graft. The Examiner further argued that Gregory provides a general motivation to combine by teaching the need for ureter tissue graft and that the reference cannot be attacked individually when the obviousness rejection is based on consideration of all (pages 4 and 5 of the final Office Action).

Appellant respectfully disagrees with the Examiner's characterization of the references and Dr. Tanagho's statements. First, Appellant has previously argued and Dr. Tanagho has attested in paragraphs 6-12 in Declaration I that there is no motivation to combine the teaching of the cited references, because of the different purposes the

methods in the art are intended for and the different results these methods lead to. On the other hand, the Examiner's assertion of a general desire in choosing tissue of the same type for making matrix graft to repair a damaged tissue finds no specific support in any of the three references when viewed together and is therefore a motivation apparent only in the hindsight. Secondly, Declaration I has consistently discussed all three cited references together and never considered any one of them outside the context of the others.

Appellant thus contends that, on the point of motivation to combine, the totality of evidence weighs in favor of Appellant.

ii. Reasonable Expectation of Success

Regarding the reasonable expectation of success, the Examiner argued, on page 5 of the final Office Action, that Appellant's contention of differences in tissue types and properties is "a mere allegation" and "not persuasive," because "Applicants fail to point out and demonstrate the differences." This statement is a complete mischaracterization of the evidence presented by Appellant and an inappropriate treatment of the evidence. The differences in various tissue types as well as their distinct biological functions and structural characteristics are explained in detail in Declaration I. As an example, in paragraph 14 of Declaration I, it is stated that, "[t]here is a large number of different types of tissues present in a human body, and that the tissues differ drastically in terms of strength, elasticity, and porosity of the cellular matrix. For instance, heart valves are a type of highly specialized tissue in that the tissue is nearly acellular except for a thin external layer of cells that can be readily removed by a variety of treatment methods to achieve a thick, dense, and relatively stiff matrix. In contrast, the intact matrix of smooth muscles such as that forms ureter or urethra provides a waterproof sheath with much higher flexibility." Thus, Appellant's contention should not be challenged on the basis of the alleged lack of discussion regarding the differences in different tissue types.

Because the differences in tissue types have been presented as evidence by way of an expert's declaration instead of attorney argument, because these differences are well known facts, and particularly because Dr. Tanagho indeed provides specific explanations of these structural and physical differences in Declaration I (*e.g.*, in paragraph 14), the Examiner cannot simply dismiss the declaration as unpersuasive for being a mere allegation, without offering any contradictory evidence or objective reasons.

Appellant thus contends that, on the point of reasonable expectation of success, the totality of evidence weighs in favor of Appellant.

iii. Unexpected Properties

The Examiner's inappropriate treatment of Declaration I continues on pages 5-6 of the final Office Action, where the Examiner challenged the declaration on the following grounds: (1) the declaration appears to be the opinion of one of the inventors; (2) there are no data comparing the claimed invention and the closet prior art; (3) the unexpected results are based on use in only one patient; and (4) there are no quantitative experimental data. Appellant contends that these are not proper bases for the Examiner to challenge Declaration I.

First of all, the Examiner cannot simply disregard a declarant's assertion of unexpected results merely because the declarant is one of the inventors or there is insufficient evidence on the record that supports the assertion. In the case of *In re Soni* (34 USPQ2d 1684, Fed. Cir. 1995), the claimed composition was rejected for obviousness. In the specification, the applicant showed improved properties of the composition over the art and asserted that such improvement amounted to unexpected results. The court reversed the rejection, stating that, "when an applicant demonstrates *substantially* improved results, ... and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *Soni*, at 1688, emphasis in original. In the present case, Appellant has indeed provided experimental evidence that the matrix graft the present inventors created performs

substantially better than any material known in the art prior to this invention, particularly in animal studies (see more detailed discussion in the paragraph below). Appellant has also asserted that the performance of the claimed matrix graft amounted to unexpected results, for example, in Declaration I. Since the fact pattern of the present application is so closely in parallel with that of *Soni*, Appellant does not believe that the Examiner can properly dismiss the asserted unexpected results "*in the absence of* evidence to the contrary."

Secondly, Appellant contends that the unexpected properties of the claimed matrix graft described in Declaration I are not merely "a statement of one inventor's opinion" without any evidentiary support. To this end, a supplemental Rule 132 declaration by Dr. Tanagho ("Declaration II") was submitted along with Appellant's response mailed July 31, 2006, to address the Examiner's attack on Declaration I, namely, the Examiner's assertions of success in only one patient and lack of comparative or quantitative data demonstrating the unexpected properties of the claimed matrix graft of this invention.

Regarding the successful repair of ureter/urethra in human patients, Dr. Tanagho attests,

> Contrary to the Examiner's assertion, the present inventors have so far performed on at least 12 human patients surgical procedures similar to that described in my previous declaration using the claimed matrix graft of this invention. In each case, the procedure has led to dramatic improvement in patient's condition as indicated by X-ray imaging and urine flow rate measurement. Thus, the extraordinary properties and unexpected success of the claimed matrix graft are not merely my personal opinion; they are facts proven by a multitude of clinical studies. (paragraph 5 of Declaration II)

Thirdly, Dr. Tanagho also explains in Declaration II why it is not possible to provide data directly comparing the properties of the claimed graft of this invention and that of the matrix of the art:

> In direct contrast with the matrix graft of this invention, which is derived from ureter or urethra smooth muscle tissue, the references by Bishopric and Goldstein teach the making of an acellular collagenous matrix derived from different tissue types, for example, heart valve and skin. The reference by Gregory teaches elastin extraction and purification, which leads to the disruption of the collagenous network of a tissue. For a graft material to be useful in ureter/urethra repair, the material must have a high level of structural integrity and flexibility, as well as water impermeability, such that the repaired tissue can perform its intended function, *i.e.*, to hold urine under a certain amount of pressure. The material produced by Bishopric, Goldstein, or Gregory does not meet such requirements because of the chosen tissue type or the loss of collagen, as tissue graft derived from heart valve or skin does not have the required elasticity and tissue without an intact collagen network does not have the required strength and structural integrity. Thus, no person of skill in the art would ever consider using the material described in the references for implantation on a human patient to repair damaged ureter or urethra tissue. The type of comparative data the Examiner has asked for simply cannot be obtained for ethical reasons. (paragraph 6 of Declaration II)

Dr. Tanagho disagrees with the Examiner that no quantitative data were presented in his earlier declaration by pointing out that results of several animal experiments quantitatively illustrating the outstanding, unexpected quality of the matrix of this invention can be found in the four references identified in paragraph 15 of Declaration I. He further explains, "[i]nsofar as the surgical repair of human ureter or urethra is concerned, quantitative data are not a preferred means to evaluate the effectiveness of the procedure. Because patient's overall physical condition (age, general health, *etc.*) as well as the extent and severity of tissue damage can vary significantly from individual to individual, quantitative data can provide only limited useful information. Moreover, surgical retrieval of post-implantation matrix graft is often necessary in order to obtain quantitative data for assessing the effectiveness of the matrix

graft. Such retrieval, however, can be performed ethically in animals only and not in human patients." See paragraph 6 of Declaration II.

Because each of the Examiner's specific concerns pertaining to Declaration I has been fully addressed, it is respectfully submitted that Appellant has properly established, by way of Dr. Tanagho's declarations, that the matrix graft of this invention has extraordinary properties and is surprisingly effective in its use for repair of ureter or urethra. These unexpected properties and results cannot be gleaned from the three cited references even when they are viewed together.

Accordingly, even if *prima facie* obviousness is established, it has been effectively rebutted by evidence presented in Declarations I and II.

iv. Additional Points Raised in the Advisory Action

The Advisory Action mailed August 15, 2006, raises two additional points: first, the Examiner asserts that Appellant's arguments regarding quantitative data are unpersuasive because the Examiner believes that paragraph 15 of Declaration I (which identifies the references where quantitative data are present) is incomplete; and second, the Examiner finds Declaration II unpersuasive because the statements therein "are not backed up by actual proof." In particular, the Examiner remains unconvinced by "the argument that the material 'in the prior art' is not suitable for use as Applicants have used their invention," because "there is no evidence that the applied prior art would not function in the manner claimed."

With regard to the first point, a careful review of Declaration I reveals that paragraph 15 therein is complete. Although there is nothing missing from Declaration I, paragraphs 17-20 have been inadvertently assigned the wrong numbers: they should have been numbered 16-19. Thus, paragraph 15 of Declaration does correctly identify the four references in which quantitative data in animal studies are presented. Moreover, these references have previously been made of record as Exhibits 5-8 of Appellant's response

mailed May 3, 2005. Thus, even if these references were not identified in Declaration I, the Examiner should have already considered them.

Insofar as the second point is concerned, the Examiner appears to again question the credibility of Dr. Tanagho's declaration without providing any objective reason or evidence to repudiate Dr. Tanagho's declaratory statements. In paragraph 6 of Declaration II, Dr. Tanagho explains in detail that, because of the differences in tissue types and treatment methods, the material obtained from Bishopric, Goldstein, or Gregory would lack the required strength, flexibility, and structural integrity and therefore could not function as the matrix graft of this invention for the intended purpose: repair damaged ureter or urethra. The Examiner dismisses Dr. Tanagho's statements, however, by a mere conclusory assertion that the statements are not persuasive without "actual proof." Appellant contends that it is inappropriate for the Examiner to dismiss an expert's declaration without offering an explanation supported by specific evidence and/or objective reasons.

7. Summary

In light of the foregoing discussion, Appellant contends that the obviousness rejection under 35 U.S.C. §103 is improper and respectfully requests its withdrawal.

Respectfully submitted,

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VIII. CLAIMS APPENDIX

24. An insoluble elastic matrix graft for repairing ureter or urethra smooth muscle having the following properties:

(i) the matrix graft is derived from ureter or urethra smooth muscle tissue;

(ii) the matrix graft is impermeable to urine;

(iii) the matrix graft consists essentially of an intact framework of collagen and elastic fibers that is free of cell contents; and,

(iv) the framework permits growth of muscle cells within the framework.

25. A matrix graft in accordance with claim 24, said matrix graft being prepared from tissue isolated from an animal selected from the group consisting of rat, rabbit, hampster, dog, pig and human.

26. A matrix graft in accordance with claim 24, said matrix graft being prepared from tissue isolated from an animal selected from the group consisting of rat, rabbit, hampster, dog, pig and human, and indicating essentially no cell nuclei when stained with a dye selected from the group consisting of trichrome, H&E, α-actin and PGP.

27. A matrix graft of claim 24 wherein the matrix graft is prepared using a combination of exogenous detergents and enzymes.

28. A matrix graft of claim 24 wherein the matrix is treated with a nuclease to remove nucleic acid.

IX. EVIDENCE APPENDIX

This appendix contains a copy of each of (1) a declaration by Dr. Emil Tanagho, which was submitted on December 16, 2005, pursuant to 37 C.F.R. §1.132 and entered into the record as indicated on page 5 of the Final Office Action mailed March 6, 2006; (2) a supplemental declaration by Dr. Emil Tanagho, which was submitted on July 31, 2006, pursuant to 37 C.F.R. §1.132 and entered into the record as indicated on page 1 of the Advisory Action mailed August 15, 2006; and (3) references filed as Exhibits 2-8 with Appellant's response of May 3, 2005.

X. RELATED PROCEEDINGS APPENDIX

None.

Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2006

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 250

Complete if Known	
Application Number	10/052,889
Filing Date	January 18, 2002
First Named Inventor	Tanagho, Emil A.
Examiner Name	Prebilic, Paul B.
Art Unit	3738
Attorney Docket No.	02307E-080710US

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 20-1430 Deposit Account Name: Townsend and Townsend and Crew LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____	-20 or HP = _____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____	-3 or HP = _____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims — Fee ($): _____ Fee Paid ($): _____

3. APPLICATION SIZE FEE

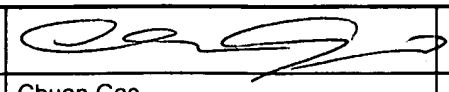
If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 =	_____ / 50 =	_____ (round up to a whole number) x	_____	= _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Filing a brief in support of an appeal	250

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 54,111	Telephone 415-576-0200
Name (Print/Type)	Chuan Gao		Date December 1, 2006